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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/057,753 | 01/23/2002 | Sergei Bavykin | 0003/00377 | 9563 |

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| EXAMINER | |
|---|---|
| KIM, YOUNG J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | |

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/057,753 | BAVYKIN ET AL. | |
| | Examiner | Art Unit | |
| | Young J. Kim | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office Action is responsive to the Amendment received on October 18, 2004.

### *Preliminary Remark*

Upon careful review of the instant application and the co-pending application 09/751,651, the instant non-final rejection is necessitated.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims 1-13 and 16-18 under 35 U.S.C. 102(e) as being anticipated by Bavykin et al. (US 2003/0096229 A1), now a U.S. Patent No. 6,818,398 B2 (issued November 16, 2004), made in the Office Action mailed on July 14, 2004 is ***maintained*** for the reasons of record.

Applicants' arguments presented in the form of Declaration under 37 CFR 1.131 in the Amendment received on October 18, 2004 have been fully considered but they are not found persuasive because declaration under 37 CFR 1.131 does not overcome 102(e) reference rejection when said reference (U.S. Patent) is ***also*** claiming the embodiment the reference is being relied upon (See MPEP 705).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Bavykin et al. (US 2003/0096229 A1) in view of Sheldon et al. (U.S. Patent No. 4,617,261, issued October 14, 1986), made in the Office Action mailed on July 14, 2004 is ***maintained*** for the reasons of record.

Applicants' arguments presented in the form of Declaration under 37 CFR 1.131 in the Amendment received on October 18, 2004 have been fully considered but they are not found persuasive because declaration under 37 CFR 1.131 does not overcome 102(e) reference rejection when said reference (U.S. Patent) is ***also*** claiming the embodiment the reference is being relied upon (See MPEP 705).

***New Grounds***

Claims 1-12, 14, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirzabekov et al. (U.S. Patent No. 5,981,734, November 9, 1999, filed July 17, 1997) in view of Guillet et al. (WO 99/22020, published May 6, 1999).

Mirzabekov et al. disclose a method of labeling DNA or RNA, wherein said method involves the following steps:

(a) generating a free aldehyde group on a DNA via process of depurination (column 4, lines 34-35) or on an RNA via process of oxidation of the 3' terminal ribonucleoside with sodium periodate (column 4, lines 36-37);

(b) the free-aldehyde group of the DNA or RNA is reacted with hydrazine (primary amine) of the fluorescent labels via nucleophilic addition reaction (column 4, lines 37-39; column 5, lines 5-6), thereby producing a labeled DNA or RNA.

The resulting hydrazone bond is disclosed as being stabilized by *reduction* with sodium cyanoborohydride (column 4, lines 39-40), and particularly, $NaCNBH_3$ (column 3, lines 8-9).

With regard to claim 4, Mizabekov et al. disclose that ethylenediamine was shown to be "particularly effective" in the quantitative scission of depurination of DNA, wherein ethylenediamine with depurinated DNA sites also introduced a reactive primary amino group that is subsequently used for fluorescent labeling by reaction with commercially available activated fluorophores (column 6, lines 16-21).

With regard to claim 7, as the fluorescent labels comprising hydrazine group is reacted with the free aldehyde group, the step reducing the condensation product and cross-linking the reduced condensation product with a label is necessarily achieved in one reaction step.

Mirzabekov et al., in generating the free aldehyde group on the DNA or RNA do not employ the reagents hydrogen peroxide in combination with the coordination complex recited in claim 3.

Guillet et al. disclose a method of generating free redicals in nucleic acid molecules (DNA or RNA) via free-radical mechanism (page 3, lines 29-30; page 8, line 24). Guillet et al., in generating free radicals in nucleic acid molecules, employ $\gamma$ irradiation (page 14, lines 3-5;

page 15, lines 17-20), as well as chemical reagents such as hydrogen peroxide (page 16, lines 4-5). Guillet et al. also disclose that it is common to add catalysts/accelerators to hydrogen peroxide to improve the yield of free radicals, particularly Fenton's reagents ($Fe^{2+}/H_2O_2$) (page 18, lines 3-4; page 33, lines 24-28), catalyzing the reaction as recited below:

$$H_2O_2 + H^+ + Fe^{2+} \rightarrow {}^{\bullet}OH + H_2O + Fe^{3+}$$

The generation of the free radicals (i.e., reaction condition) is disclosed as being conducted at room temperature (thus below the boiling point of water as well as being between 0°C and 95°C (page 20, lines 15-16).

Guillet et al. disclose that single stranded DNA molecules from Sigma®, which are denatured in 1.02% aqueous solution were employed (page 20, lines 6-10). While Guillet et al. are not explicit the description of the aqueous solution containing the single-stranded DNA molecules, it is assumed that the aqueous solution contains denaturing (or double-strand weakening) agent.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made employ the well-known reaction reagents of Guillet et al. to produce nucleic acids comprising free aldehyde group of Mirzabekov et al. for the following reasons.

Mirzabekov et al., while not explicit, disclose a critical feature of their invention, which would have motivated a one of skill in the art:

"A feature of the invention is the ***chemical modification*** of the terminus or internal residues of the molecules for ***subsequent*** attachment of different labels. An ***advantage*** of the invention is that the ***efficiency*** of the labeling is independent of the oligonucleotide length." (column 2, lines 23-27)

Mizabekov et al. continue :

"A feature of the invention is direct fluorescent labeling of DNA and RNA. An ***advantage*** of the invention is that the labeling method can be applied to both DNA and RNA, either isolated from cells or synthesized..."

The critical feature is disclosed as, "modifying the nucleic acid molecules to ***create a region having an active center, and contacting a dye to the active center so as to cause attachment of said dye to the active center***. One embodiment of the method is modifying the ***nucleic acid to create a nucleophilic region (e.g., a region containing a primary amino group***)...and ***contacting an activated fluorescent dye with the region so as to cause addition of the fluorescent label to the region***." (column 2, line 62 through column 3, line 4).

While Mirzabekov et al. are not explicit in every well known method which would produce a nucleophilic reagion (or free radical containing region) on a nucleic acid molecules, given such disclosure, one of ordinary skill in the art would have been reasonably motivated to employ well-known methods of producing free aldehyde region (or free radical region) on a nucleic acid, such as Fenton reagents disclosed by Guillet et al., employing hydrogen peroxide with transition metal ion complex to arrive at the claimed invention.

One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success at producing this combination as Mirzabekov et al. make clear that so long as free aldehyde region (or free radical region) is produced in a nucleic acid molecule, the reduction of said region through amine and fluorescently labeling would have been produced.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirzabekov et al. (U.S. Patent No. 5,981,734, November 9, 1999, filed July 17, 1997) in view of Guillet et al. (WO 99/22020, published May 6, 1999) as applied to claims 1-12, 14, 16, and 17 above, and further in view of Fuller et al. (U.S. Patent No. 5,314,595, issued May 24, 1994).

The teachings of Mirzabekov et al. and Guillet et al. have already been discussed above.

Mirzabekov et al. and Guillet et al. do not explicitly discuss the well-known denaturing reagents of double-stranded nucleic acid recited in claim 15.

Fuller et al. evidences that reagents such as urea are well-known DNA denaturing reagent, commonly employed in biotechnology art (column 4, lines 55-56).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ any of well-known denaturing reagents, such as that of Fuller et al. to produce a single stranded nucleic acid molecule for labeling method of Mirzabekov et al. and Guillet et al. for the following reasons.

The method of Mirzabekov et al. and Guillet et al. is drawn to a method of labeling a single-stranded nucleic acid molecules (such as DNA or RNA). Since the artisans employ single-stranded nucleic acids in their labeling method, one of ordinary skill in the art at the time the invention was made would have been clearly motivated to employ any of the well-known denaturing reagents, such as urea of Fuller et al., to first denature the double stranded nucleic acid prior to subjecting them to the single stranded nucleic acid labeling method of Mirzabekov et al. and Guillet at al. with a reasonable expectation of success.

Therefore the invention as claimed is *prima facie* obvious over the cited references.

***Double Patenting***

The rejection of claims 1-13 and 16-18 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of copending application no. 09/751,654, now issued as U.S. Patent No. 6,818,398 B2, issued on November 16, 2004, made in the Office Action mailed on July 14, 2004 is withdraw in view of the filing of Terminal Disclaimer, filed on October 18, 2004.

The rejection of claims 14 and 15 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 09/751,654, now issued as U.S. Patent No. 6,818,398 B2, issued on November 16, 2004, in view of Sheldon et al. (U.S. Patent No. 4,617,261, issued October 14, 1986), made in the Office Action mailed on July 14, 2004 is withdrawn in view of the filing of Terminal Disclaimer, filed on October 18, 2004.

***Conclusion***

No claims are allowed.

***Inquiries***

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
3/19/05

YOUNG J. KIM
PATENT EXAMINER

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